Introduction to Medication Treatment for Opioid Use Disorder

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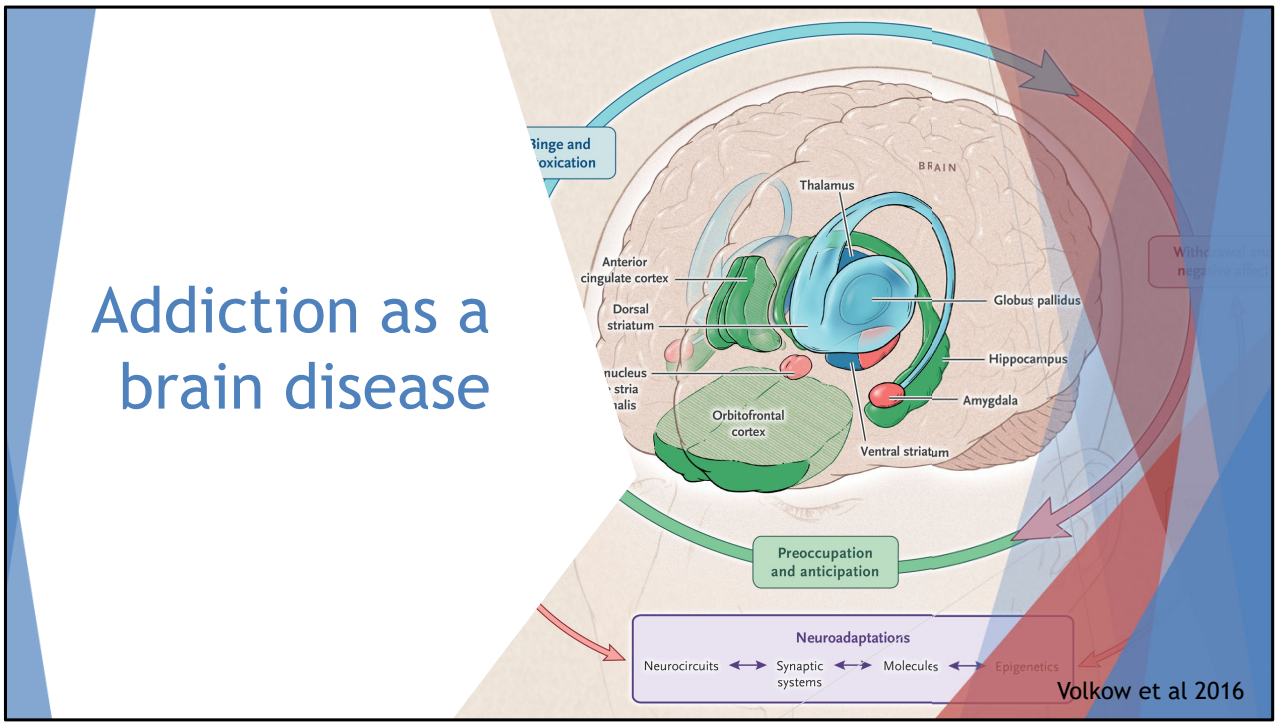
Disclosures

- None
- Views my own

Addiction as a brain disease

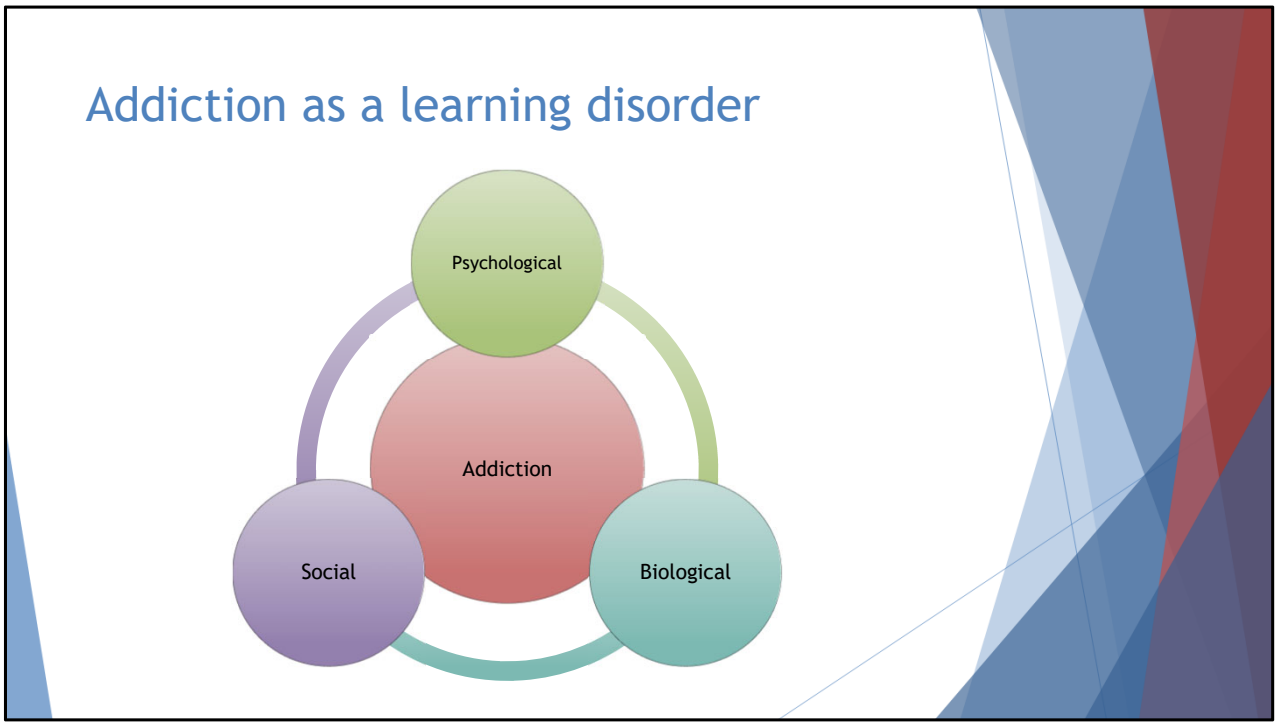


- Health providers often describe addiction as a brain disease. What does this mean?
- It means that studies show that the structure and process of the brain is altered in addiction. Just as in diabetes the normal functioning of the pancreas is disrupted or in heart disease the normal of the functioning of the heart is altered.
    - In particular, studies show changes in the reward circuits (nucleus accumbens and the dorsal striatum) and the parts of the brain responsible for controlling impulses (prefrontal cortex).
    - Scientists think these changes explain the compulsive consumption of drugs and the impulsive actions in addiction. In other words, people with addiction will do and say things they wouldn't normally do or say because normal brain processes are disrupted.
- These brain changes show that it's not helpful to just tell people with addiction to quit it.
    - No more helpful to tell someone with diabetes, "use your

willpower to fix your blood sugar" than it is to tell someone with addiction "use your willpower to fix your brain"
        - That's not to say people with addictions are robots programmed to use drugs- people still have agency and the ability to recover. However, we give people the best chance to recover when we address the biology of addiction.

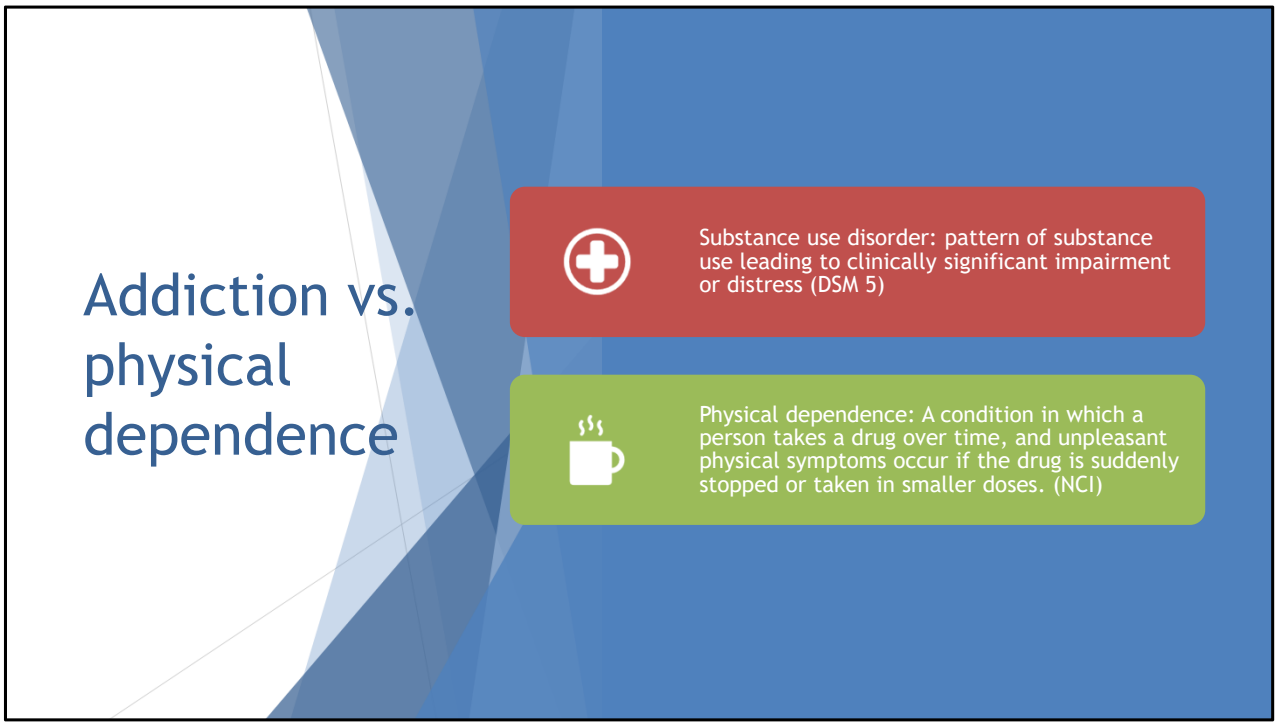
- Brain disease model of addiction acknowledges that social and psychological factors play a role in the development of addiction and must be addressed in the treatment of addiction.

Image from: Volkow ND, Koob GF, McLellan AT. Neurobiologic Advances from the Brain Disease Model of Addiction. *N Engl J Med*. 2016;374(4):363–371. doi:10.1056/NEJMra1511480



- Other providers prefer to think of addiction as a learning disorder.
- This approach does not deny that important brain changes that take place in addiction. Rather this approaches places greater emphasis on understanding and addressing the social and psychological factors that lead to the biological changes we see in addiction.
- The fact that there are psychological and social factors that influence addiction does not make it special or different from other disease.
  - There are social and psychological factors that increase people's risk of diabetes also. The diet you were raised on as a kid can affect your risk for diabetes. The neighborhood you live in, which may not have a lot of outdoor spaces for activities, may affect your risk for diabetes.
  - In addiction, genetic factors can also affect you risk. A family history and having traumatic childhood experiences can increase risk for addiction.
  - **Bottom line is : Proponents of the brain disease model and of the learning disorder model agree that medication treatment with**

available psychosocial services is the best way to treat opioid addiction.

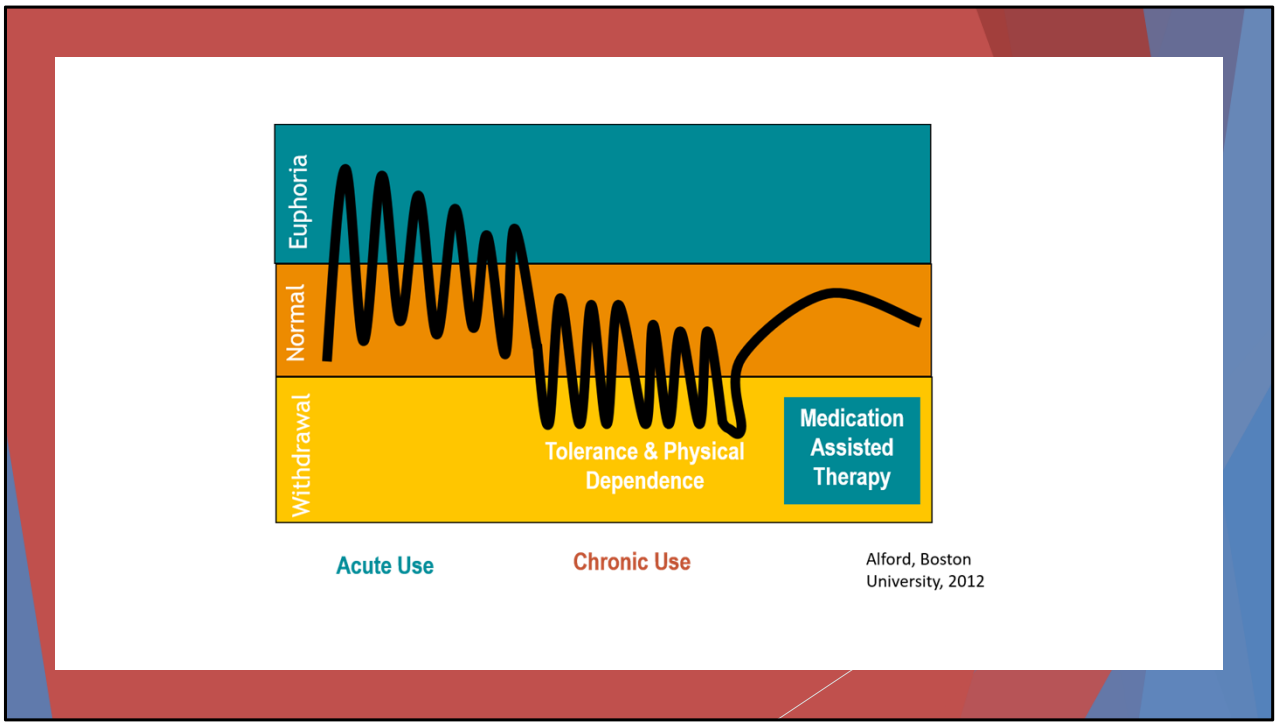


- It's important to understand the difference between addiction and physical dependence, since this is a source of confusion and misinformation.
- Physical dependence is a condition in which a person takes a drug over time and unpleased withdrawal symptoms occur if the drug is suddenly stopped or taken in smaller doses.
    - Many of us have some physical dependence on caffeine. That doesn't mean we're addicted to caffeine. Many prescribed medications lead to physical dependence including many anti-depressants. Again, that doesn't mean people are addicted to these medications.
- Addiction or substance use disorder (the preferred term) is a pattern of behavior around drug use that lead to clinically significant impairment or distress.
    - Addiction is a pattern of behavior. There's no test for addiction. It is diagnosed through an in-depth assessment by a trained professional.
- In the context of opioid addiction, this distinction is very important.
    - Someone who has been taking opioids for a long time to treat pain is likely physical dependent, but that doesn't necessarily meant that person has an addiction disorder. Babies born to mothers who used opioids may be born physically dependent to these opioids, but these babies are not addicted.
    - People receiving treatment for addiction with medication may continue to

be physically dependent on opioids. That leads to confusion and misinformation that these people are addicted to the medications. In fact, people are treatment continue to be dependent, but no longer meat the criteria for substance use disorder.

- Review criteria
- Note that tolerance and withdrawal are part of these criteria but do not count if opioids are being taken under medical supervision.
- Someone who is in treatment for opioid disorder will have physical dependence but that does not count towards the criteria. That person will also generally not meet the other criteria for opioid use disorder.

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:



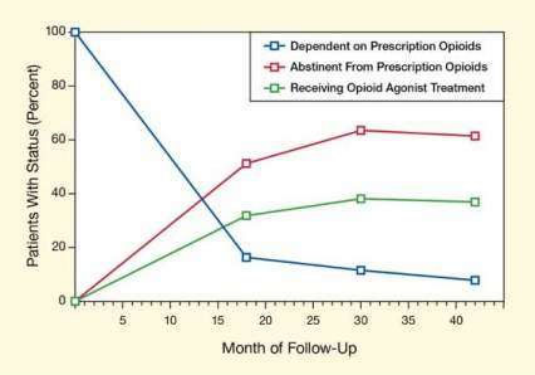
- This is a very simplified graph of the course of opioid use in a person who develops an opioids use disorder.
- Opioids that are used illicitly are typically short-acting opioids that are often injected or snorted. The opioids quickly reach the brain, they provide intense activation of opioid receptors that cause euphoria.
    - The intense activation of opioid receptors also causes respiratory depression, which is how people die of overdoses.
    - After the intensive activation, these short-acting opioids then quickly fall off, creating the extreme rises and falls.
    - Over time, this pattern leads to tolerance (meaning the same doses of opioids won't have the same effect) and physical dependence (meaning the person experiences withdrawal symptoms between use)
- The two main medication used in treatment are long-acting opioids that don't produce these peaks and falls. They provide enough opioid activation to keep people from experience withdrawal and to reduce cravings for opioids.
    - If the person does use a short-acting opioid like heroin during treatment, the long-acting opioids will block the effect, reducing the chance that the person will overdose.
- It's important to note that many people who use opioids in this way never develop

an opioid use disorder or are able to stop using without treatment.

- The science is not settled on why some people develop addiction disorders requiring treatment and others don't. It's likely a result of interaction of genetic and psycho-social factors that make some people more vulnerable to addiction when exposed to certain drugs.

Medication treatment works

- 4 week bup-nx “detox”
  - 7% successful after 8 weeks
  - No different with counseling
- 12 week bup-nx stabilization
  - 49% successful outcome at week 12
  - 8% successful 8 weeks after taper
  - No difference with counseling
- 18 months follow up
  - 79% abstinent with medication
  - 38% abstinent without medication
- 42 months follow up
  - 80% abstinent with medication
  - 51% abstinent without medication



Weiss et al, 2011; Weiss et al 2015.

- There are dozens of studies providing evidence that medication treatment for opioid use disorder is effective at reducing illicit and risk drug use. I will talk through one study that is particularly illuminating.
- In this study people with OUD were first given a 4 week “detox.” Within 8 weeks of detox, 93% of the people in the study returned to illicit opioid use. Getting counseling didn’t make a difference.
  - Those that return to opioid use (almost everyone) were then given 12 week buprenorphine treatment. At the end of that about half had successful outcomes. 8 weeks later, again about 92% were successful. Getting counseling didn’t make a difference.
  - Researchers checked back with participants after 18 months and again 42 months. The people who were on treatment had an abstinence rate of about 80% whereas the ones not on treatment had a rate of 38% at 18 months and 51% at 42 months.
- **Bottom lines**
  - **1. Just detoxing people doesn’t reduce opioid use, even with counseling.**
  - **2. Treatment is very efficacious in reducing opioid use.**
  - **3. Many return to illicit use when treatment is cut off as a particular time point. As with other chronic disease, people should stay on as long as**

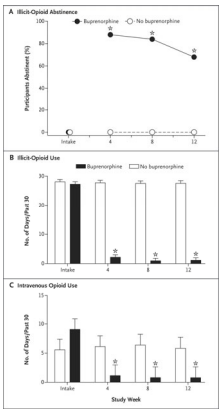
they are getting benefit from it (insulin for diabetes or beta blockers for heart disease)

- **4. There's no detectable difference with counseling (doesn't mean counseling isn't important).**

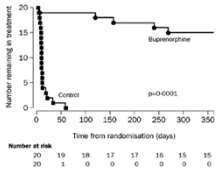
Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011;68(12):1238–1246. doi:10.1001/archgenpsychiatry.2011.121

Weiss RD, Potter JS, Griffin ML, et al. Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. *Drug Alcohol Depend*. 2015;150:112–119. doi:10.1016/j.drugalcdep.2015.02.030

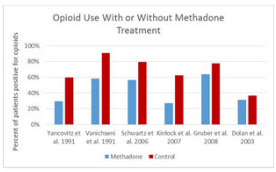
Many studies support the use of medications in treatment



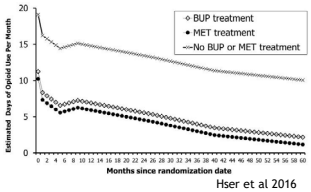
Sigmon et al 2016



Kakko et al 2003



NIDA 2018



Hser et al 2016

- We could talk all day about studies with similar findings.
- There are also studies that show that medication treatment reduces reduces infections risk (HIV/HCV) and criminal activity

Hser YI, Evans E, Huang D, et al. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. *Addiction*. 2016;111(4):695–705. doi:10.1111/add.13238

Sigmon SC, Ochalek TA, Meyer AC, et al. Interim Buprenorphine vs. Waiting List for Opioid Dependence. *N Engl J Med*. 2016;375(25):2504–2505. doi:10.1056/NEJMc1610047

Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet Lond Engl*. 2003;361(9358):662-668. doi:10.1016/S0140-6736(03)12600-1.

Yancovitz SR, Des Jarlais DC, Peyser NP, et al. A randomized trial of an interim methadone maintenance clinic. *Am J Public Health*. 1991;81(9):1185-1191.

Vanichseni S, Wongsuwan B, Choopanya K, Wongpanich K. A controlled trial of methadone maintenance in a population of intravenous drug users in Bangkok: implications for prevention of HIV. *Int J Addict*. 1991;26(12):1313-1320.

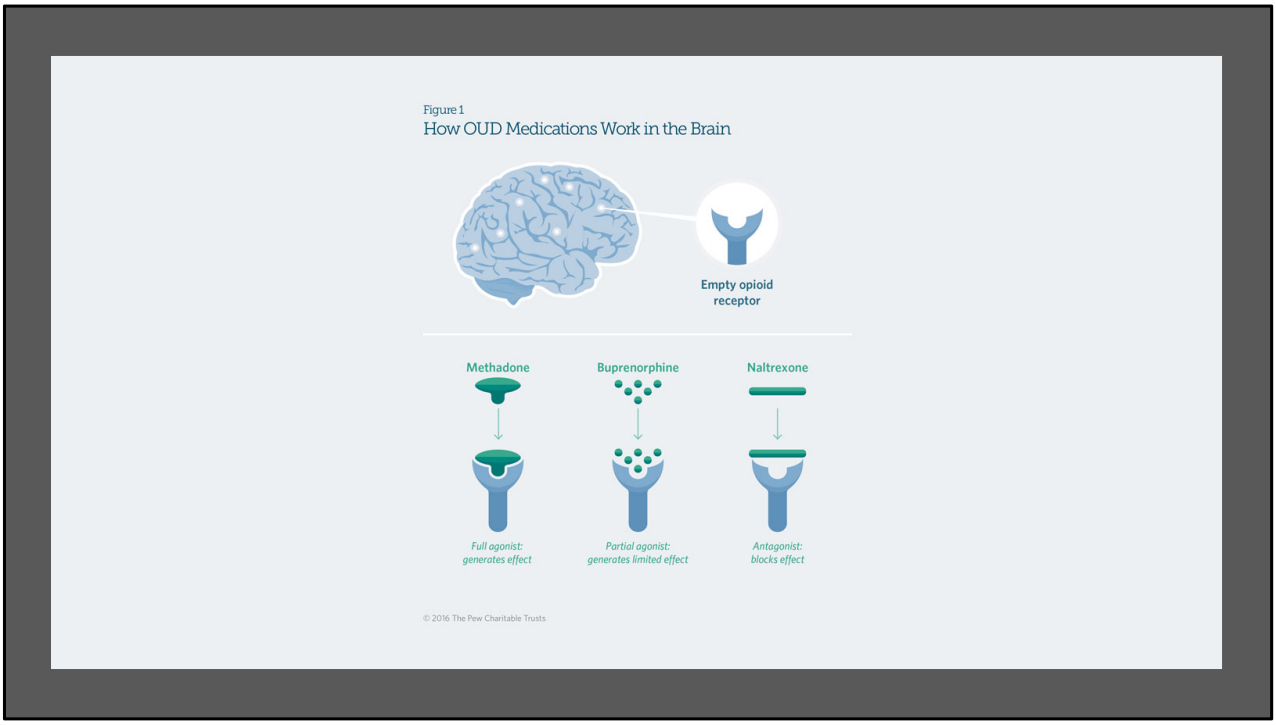
Schwartz RP, Highfield DA, Jaffe JH, et al. A randomized controlled trial of interim methadone maintenance. *Arch Gen Psychiatry*. 2006;63(1):102-109. doi:10.1001/archpsyc.63.1.102.

Kinlock TW, Gordon MS, Schwartz RP, O'Grady K, Fitzgerald TT, Wilson M. A randomized clinical trial of methadone maintenance for prisoners: results at 1-month post-release. *Drug Alcohol Depend*. 2007;91(2-3):220-227. doi:10.1016/j.drugalcdep.2007.05.022.

Dolan KA, Shearer J, MacDonald M, Mattick RP, Hall W, Wodak AD. A randomised controlled trial of methadone maintenance treatment versus wait list control in an Australian prison system. *Drug Alcohol Depend*. 2003;72(1):59-65.

Gruber VA, Delucchi KL, Kielstein A, Batki SL. A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug Alcohol Depend*. 2008;94(1-3):199-206. doi:10.1016/j.drugalcdep.2007.11.021.

Methadone treatment image from :https://www.drugabuse.gov/publications/research-reports/medications-to-treat-opioid-addiction/efficacy-medications-opioid-use-disorder



- There are three medications approved in the US for the treatment for opioid use disorder
- These graphic just shows how medications for treat opioid use disorder stick to opioid receptors and block them so short-acting opioids like heroin can't get to the receptors.
- Methadone is a full opioid agonist so it activate the opioid rector while blocking it. Buprenorphine is a partial agonist so it partially activates the receptor. And naltrexone is an antagonist which means it does not activate the receptor at all.

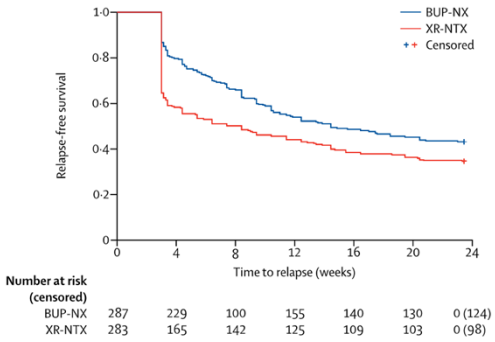
	Methadone	Buprenorphine	Naltrexone
Formulations	Oral liquid	Transmucosal pill/film, subcutaneous, injectable	Oral pill, injectable
Brand names	Dolophine, Methdadose	Suboxone, Zubsolv, Probuphine, Sublocade	ReVia, Vivitrol
Class	Agonist (full activation of opioid receptors)	Partial agonist (diminished activation of receptors)	Antagonist (blocks opioid receptors without activation)
Effects	Reduces opioid cravings and withdrawal symptoms / blocks short-acting opioids	Reduces opioid cravings and withdrawal symptoms / blocks short-acting opioids	Blocks opioids
Availability	Opioid treatment programs	OTPs and waivered providers	No restrictions
Special issues	Daily visits	Naloxone combo	Must be abstinent

Adapted from Volkow et al 2014

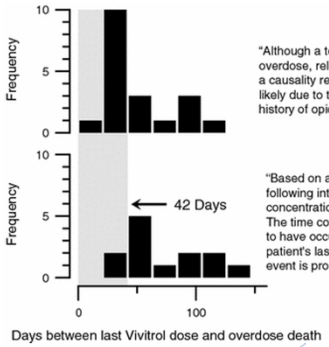
Adapted from Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-Assisted Therapies — Tackling the Opioid-Overdose Epidemic. N Engl J Med [Internet]. 2014 May 29;370(22):2063–6. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMp1402780

Naltrexone

Lower retention



Possible OD risk



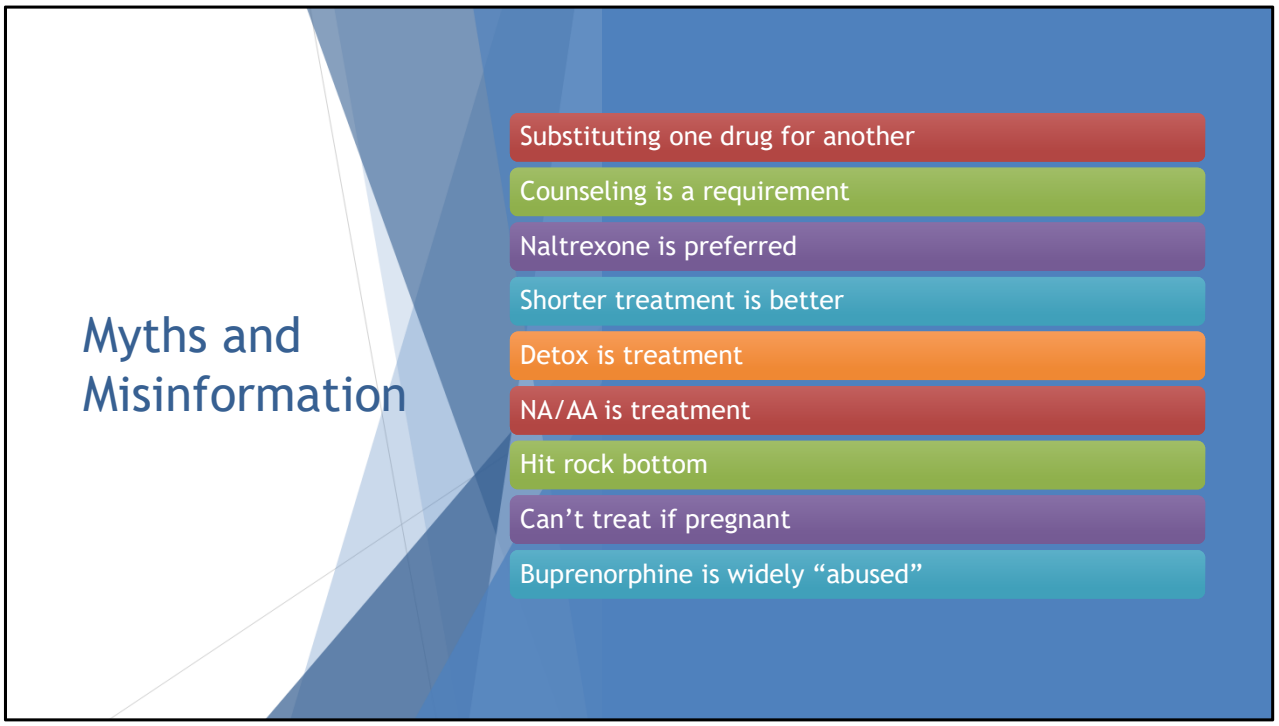
"Although a temporal relationship exists between overdose, relapse, heroin use, and VIVITROL, a causality relationship is unlikely as it is more likely due to the patient's underlying history of opioid dependence."

"Based on a pharmacokinetic assessment of VIVITROL following intramuscular injection, average naltrexone concentrations are undetectable by 42 days. The time course of the event of overdose appears to have occurred greater than 42 days after the patient's last injection of VIVITROL. Accordingly, the event is probably not related to VIVITROL."

- Research shows many more people are lost at induction with naltrexone compared to buprenorphine.
- There is also concern that people who stop naltrexone may be at increased risk of overdose.

Lee JD, Nunes EV Jr, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet*. 2018;391(10118):309–318. doi:10.1016/S0140-6736(17)32812-X

Saucier R, Wolfe D, Dasgupta N. Review of Case Narratives from Fatal Overdoses Associated with Injectable Naltrexone for Opioid Dependence. Drug Saf [Internet]. 2018 Oct 20;41(10):981–8. Available from: http://link.springer.com/10.1007/s40264-018-0653-3



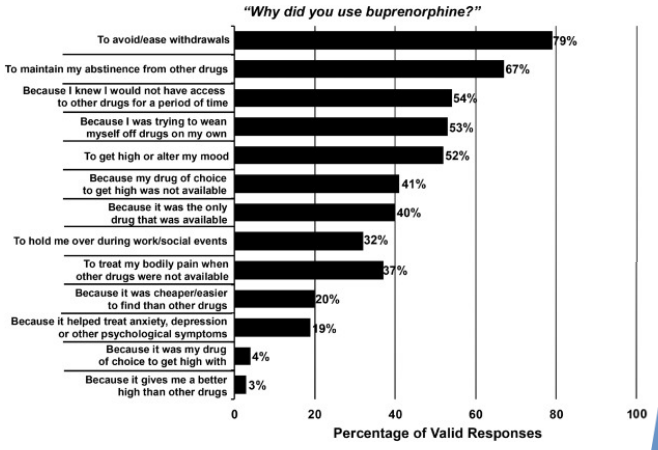
- The most common misconception is that medication treatment for OUD is just "substituting one drug for another" or that medication are a "crutch."
    - This misconception is rooted in stigma and a lack of understanding of the difference between physical dependence and addiction. People are treatment are physically dependent but don't have symptoms of addiction. The effect of medications are different from the effect of opioids used in active addiction as we've seen.
- Research shows medication treatment is effective even without counseling.
    - That doesn't mean counseling isn't important. Everyone should have access to counseling. It just means that it doesn't make sense to deny someone life-saving medication if they don't have access to counseling or aren't ready to engage in counseling.
- There's some perception (especially in criminal justice settings) that naltrexone is a superior or preferred treatment
    - Some people coming out of incarceration will be abstinent from opioids and naltrexone may be a good option.
    - However, we've seen how in on average many people do not adhere to naltrexone after induction.
    - The key is that there's no wrong path to recovery – people should have a

choice of which treatment they prefer, rather than being forced to one over another.

- There's no evidence to support limiting treatment length
    - As we saw, when people came off treatment, they returned to use.
- "Detox" or "tapering" is not treatment.
    - Evidence shows vast majority will return to use.
    - Again, people should be able to chose their path to recovery. However, we should try to make sure they are making choices best on correct information and not on views based in misinformation and stigma.
- NA/AA is also not treatment.
    - It doesn't mean it's not important or valuable. Many see it as a very valuable source of support.
- There's no evidence that people need to "hit rock bottom" in order to recover
    - We weren't able to review evidence, but it suggests the opposite. Recovery is often a long, winding road. The trauma of experiences associated with "hitting rock bottom" can be a barrier to recovery.
- Medication treatment is safe and effective in pregnancy.

Buprenorphine diversion

- Several studies have surveyed people who use drugs about diverted buprenorphine use
- Cited reasons for diverted use are consistent with therapeutic use
- 81% said they'd prefer to be prescribed buprenorphine
- Only 4% said buprenorphine was their drug of choice

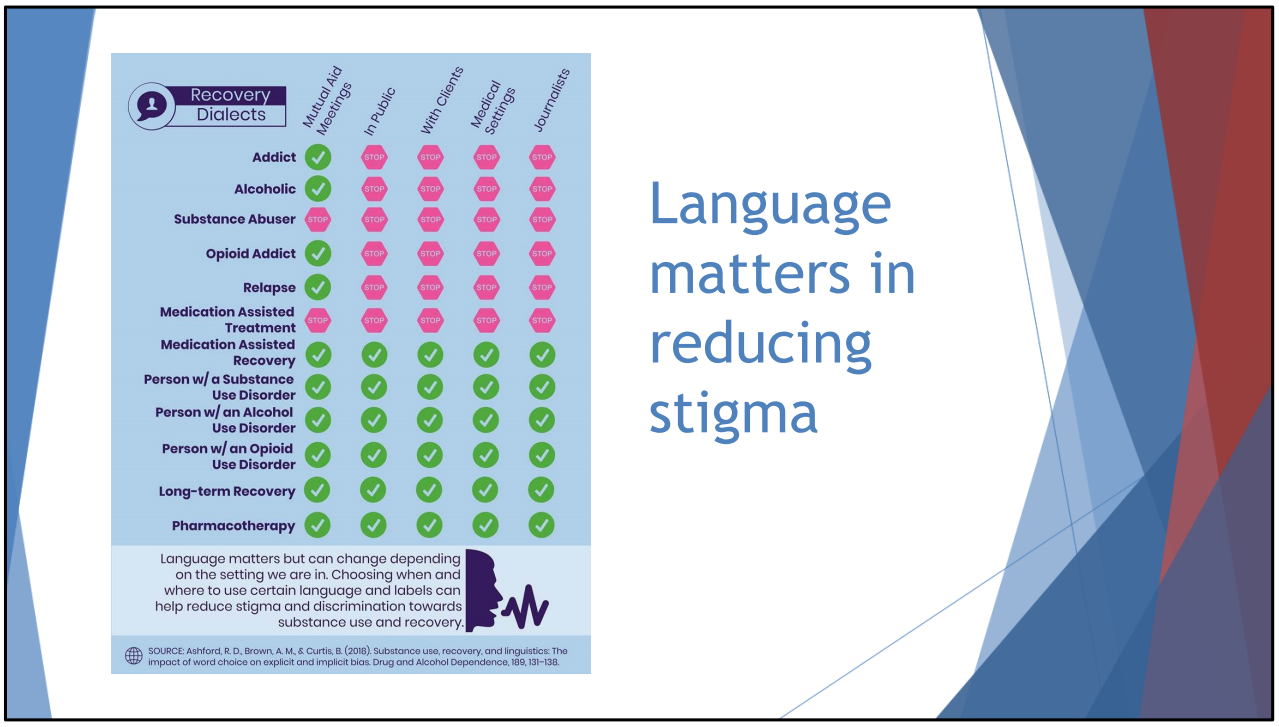


Cicero et al 2018

- Studies show illicit buprenorphine is generally not used to get high, but to treat symptoms of opioid addiction, as it would be if people could access treatment.
- I'm not saying buprenorphine diversion is OK. I'm saying research shows that buprenorphine diversion is driven by how hard it is to access buprenorphine through legitimate means.
- When payers limit access to buprenorphine (through prior authorization or other means) because they are concerned with diversion, they could be making diversion worse.

Cicero TJ, Ellis MS, Chilcoat HD. Understanding the use of diverted buprenorphine. Drug Alcohol Depend [Internet]. 2018 Dec [cited 2018 Oct 26];193:117–23. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0376871618307245

- Many providers not trained in addiction treatment and may have misinformed views (NA/AA or detox is treatment)
- Not enough waivered providers and OTPs.
- Many provider don't accept insurance (reimbursement is too low).
- Many provider have very restrictive policies like requiring counseling multiple times per week. May be appropriate for some patients, but for others may just be a burden.
- Insurers may have prior authorization and low reimbursement. Insurers don't necessarily have enough in network providers or help people find providers.
- Stigma and misinformation feeds and sustains all these barriers.



- Research shows that using certain terms can promote stigmatizing attitudes towards people with SUD.
- Review preferred terms.

Summary

- Medications are effective in reducing illicit opioid use but underutilized
- Buprenorphine and methadone are most effective medications
- Stigma and misinformation are significant barriers to medication
- Many other barriers remain